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2,5-dihydrothiophene 1,1-dioxide (Sulfolene)  
CAS Number 77-79-2

**High Production Volume (HPV) Challenge Program**

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**2,5-dihydrothiophene 1,1-dioxide (Sulfolene)**  
**CAS Number 77-79-2**

**Chevron Phillips Chemical Company LP**  
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March 2004

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## **ABBREVIATIONS**

BCF = predicted bioconcentration factor  
cm<sup>3</sup> = cubic centimeter  
CPCChem = Chevron Phillips Chemical Company LP  
EC = Commission of the European Communities  
HEW = (United States) Department of Health, Education, and Welfare  
hPa = hectopascal  
HPV = High Production Volume  
ICCA = International Council of Chemical Associations  
IUCLID = International Uniform Chemical Information Dataset  
IUPAC = International Union of Pure & Applied Chemistry  
Koc = organic carbon partition coefficients  
LC<sub>50</sub> = lethal concentration (to 50% of animals dosed)  
LD<sub>50</sub> = lethal dose (to 50% of animals dosed)  
LOAELs = lowest observed adverse effect levels  
mg/kg = milligrams per kilogram  
mg/L = milligrams per liter  
NOAELs = no observed adverse effect levels  
OECD = Organisation for Economic Cooperation and Development  
SIDS = Screening Information Data Set  
Sulfolane = tetrahydrothiophene 1,1-dioxide  
Sulfolene = 2,5-dihydrothiophene 1,1-dioxide  
USEPA = United States Environmental Protection Agency  
µg = micrograms

## **I. EXECUTIVE SUMMARY**

Chevron Phillips Chemical Company LP (CPChem) is committed to fulfilling the High Production Volume (HPV) commitments it made under the United States Environmental Protection Agency (USEPA) HPV Challenge Program on February 14, 2001. As part of this commitment, CPChem has volunteered to assess the health and environmental hazards, including selected physicochemical characteristics of 2,5-dihydrothiophene 1,1-dioxide (CASN 77-79-2), commonly known and referred to hereafter as Sulfolene. Sulfolene is a clear, solid, odorous organosulfur compound (C<sub>4</sub>H<sub>6</sub>O<sub>2</sub>S) used as a specialty solvent in petroleum refining and as a chemical intermediate in the production of tetrahydrothiophene 1,1-dioxide (Sulfolane).

CPChem has identified data from company proprietary files, peer-reviewed literature, and/or calculated endpoints using widely accepted computer modeling programs. In fulfillment with USEPA guidance for use of read-across data (USEPA, 1999b), CPChem proposes the use of surrogate data from Sulfolane (CASN 126-33-0), a close structural analogue to Sulfolene, to fill Screening Information Data Set (SIDS) endpoint data gaps and provide additional support in our understanding of health and environmental hazards for Sulfolene and Sulfolane. In addition, Sulfolane is currently being sponsored by Japan and CPChem through the International Council of Chemical Associations (ICCA) HPV Program. Both Sulfolane and Sulfolene have a relatively narrow range of physicochemical parameters and are composed of similar function groups. Thus, these two substances are expected to demonstrate similar environmental fate profiles and ecotoxicity as well as similar mammalian toxicity. Metabolism studies in rats show that Sulfolane is metabolized via ring hydroxylation into 3-hydroxytetrahydrothiophene-1:1-dioxide (Roberts and Warwick, 1961), which is consistent with expected biotic and/or abiotic hydrolysis of Sulfolene, and supports that these analogs have a common mode of action.

Physicochemical endpoints for Sulfolene are fulfilled by using existing measured data or data calculated by the EPIWIN<sup>®</sup> computer model. No additional testing is proposed for this program. A review of the existing data for Sulfolene and Sulfolane shows that sufficient data are available to characterize environmental fate and aquatic toxicity. An estimation from a Level III fugacity model predicts that these substances will likely partition to soil and water. Ready biodegradation testing showed that both Sulfolene and Sulfolane are not readily biodegradable and have very low predicted bioconcentration factors; organic carbon partition coefficients suggest similar fate profiles in the environment and no bioaccumulation hazard for either Sulfolene or Sulfolane. Acute fish, daphnid, and algal data indicated that Sulfolene is relatively nontoxic to aquatic organisms. Fish appear to be the most sensitive species with a lethal concentration to 50% of dosed organisms (LC<sub>50</sub>) of 940 milligrams per liter (mg/L). No additional testing is proposed for environmental fate and ecotoxicity.

The considerable existing mammalian toxicity information for Sulfolene and Sulfolane demonstrates that these substances share a similar order of toxicity, regardless of the additional double bond in Sulfolene. Mammalian toxicity data demonstrates a low order

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of toxicity via oral, dermal, and inhalation routes of exposure. Genotoxicity data exist for both Sulfolene and Sulfolane, and indicate that genotoxicity is not expected. Repeated dose toxicity testing on both Sulfolene and Sulfolane showed similar results in both rats and mice, and no further repeated dose toxicity testing is required. Sulfolene has not been tested for reproductive and developmental toxicity, but, due to its close structural similarity to Sulfolane, it would be expected to be of a similar order of magnitude as Sulfolane. Given that Sulfolane is characterized for this endpoint and Sulfolene is expected to produce results of the same order of magnitude, Sulfolane can be used as a structural surrogate for Sulfolene, and no further Sulfolene testing is warranted for this endpoint.

All HPV endpoints have been satisfied for the USEPA HPV Challenge Program. Table 1 summarizes the available data for Sulfolene and Sulfolane. No further testing is proposed for the USEPA HPV Challenge Program.

**Table 1. Matrix of Available and Adequate Data on Sulfolene and Sulfolane**

Test	Sulfolene Y/N (Klimisch Score)	Sulfolane Y/N (Klimisch Score)	Testing Planned? Y/N
<b>Physical and Chemical Data</b>			
Melting Point	Y (2)	N	N
Boiling Point	Y (2)	Y (1)	N
Vapor Pressure	Y (2)	Y (1)	N
Partition Coefficient	Y (1)	N	N
Water Solubility	Y (2)	N	N
<b>Environmental Fate and Pathways</b>			
Photodegradation	Y (2)	Y (2)	N
Stability in Water (Hydrolysis)	N	Y (1)	N
Transport/Distribution	Y (2)	Y (1)	N
Biodegradation	Y (1)	Y (1)	N
<b>Ecotoxicity</b>			
Acute/Prolonged Toxicity to Fish	Y (1)	Y (1)	N
Acute Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	Y (1)	Y (1)	N
Acute Toxicity to Aquatic Plants (Algae)	Y (1)	Y (1)	N
Chronic Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	N	Y (1)	N
<b>Toxicity</b>			
Acute Toxicity (Oral)	Y (1)	Y (1)	N
Acute Toxicity (Inhalation)	Y (1)	N (4)	N
Repeated Dose	Y (2)	Y (1)	N
Genetic Toxicity <i>in vitro</i> – Gene Mutation	Y (1)	Y (1)	N
Genetic Toxicity <i>in vitro</i> – Chromosomal Aberration	Y (2)	Y (1)	N
Reproductive Toxicity	N	Y (1)*	N
Developmental Toxicity	N	Y (1)*	N

\* Reproduction/Developmental Toxicity Screen (OECD 421) was completed for Sulfolane.

**NOTE:**

*The data used to characterize the Organisation for Economic Cooperation and Development (OECD) SIDS endpoints for substances in this test plan were identified either in company proprietary files, the peer-reviewed literature, and/or calculated using widely accepted computer modeling programs. Sulfolane was used for read-across as defined by the USEPA (1999b). All data were evaluated for study reliability in accordance with criteria outlined by the USEPA (1999a). Only studies that met the reliability criteria of “1” (reliable without restrictions) or “2” (reliable with restrictions) were used to fulfill OECD SIDS endpoints. Additional data for Sulfolene and Sulfolane are also included in the IUCLID (International Uniform Chemical Information Dataset), attached in Appendices I and II. A more detailed discussion of the data quality and reliability assessment process used in developing this test plan is provided in Appendix III.*

## **II. GENERAL SUBSTANCE INFORMATION**

Sulfolene (CAS Number 77-79-2) is a commercially important product, with unique physical and chemical properties, that is used as an industrial solvent and isolated intermediate for the production of Sulfolane (CAS Number 126-33-0). Sulfolene is also used as a chemical intermediate in the production of transmission fluids.

Sulfolene is produced by the reaction of sulfur dioxide and 1,3-butadiene, and has a total production volume in the US of approximately 2 million pounds per year. Sulfolene is used commercially to remove benzene, toluene, and xylene from oil refinery streams and petroleum fuels, as well as to remove carbon dioxide from closed environments or scrubbing acids from various gas streams.

A majority of Sulfolene is subsequently hydrogenated to Sulfolane, another important solvent and close structural surrogate. Sulfolane is very well characterized from a physical/chemical, environmental, and human health point of view due to its HPV sponsorship by the ICCA and its numerous commercial applications, which include: selective solvents for liquid-vapor and aromatic hydrocarbon extractions; polymerization solvents; plasticizers, fractionation of wood tars, tall oil, and other fatty acids; textile finishing; curing agents for epoxy resins; and medicinal applications (patented and used as a vehicle for an injectable form of the drug heparin, as well as being developed as an encapsulated material for oral administration) (CPChem Internal Document, not dated; Budavari, 1989 in HSDB, 2003; Hawley, 1977 in HSDB, 2003; and Sax and Lewis, 1987 in HSDB, 2003).

## **III. STRUCTURAL SURROGATE DISCUSSION**

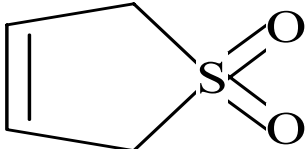
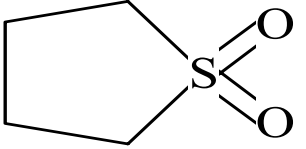
For Sulfolene, a substantial amount of data exists to characterize most of the OECD SIDS hazard endpoints and to meet the requirements of the USEPA HPV Challenge Program. However, Sulfolane also serves as a close structural surrogate to Sulfolene and adds to

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the weight of evidence in characterization of many Sulfolene physical/chemical, environmental, and human health-related endpoints.

As is shown in Figure 1, these close structural analogs differ only in the presence of a carbon-carbon double bond versus a single bond in the thiophene ring structures. Otherwise, they possess identical functional groups.

**Figure 1. Structural Comparison of Sulfolene and Sulfolane**

Sulfolene	Sulfolane
	
International Union of Pure & Applied Chemistry (IUPAC) Chemical Name: 2,5-dihydrothiophene 1,1-dioxide	IUPAC Chemical Name: Tetrahydrothiophene 1,1-dioxide
CAS Number = 77-79-2 Molecular Weight = 118.15 SMILES: <chem>O=S(=O)(CC=C1),C1</chem>	CAS Number = 126-33-0 Molecular Weight = 120.17 SMILES: <chem>O=S(=O)(CCC1),C1</chem>

Importantly, in both Sulfolene and Sulfolane the five member thiophene ring contains the strongly electron withdrawing sulphone functional group (i.e. R-SO<sub>2</sub>), which essentially lowers the activation energy needed for chemical reactions to occur at carbon atoms three and four, on the opposite side of the thiophene ring. This explains the nucleophilic ring hydroxylation at carbon number three that was observed in Sulfolane metabolism studies in rats (Roberts and Warwick, 1961). The double bond of Sulfolene is also located across from the sulphone functional group, which makes these carbon atoms at the double bond an excellent site for nucleophilic attack. Therefore, both Sulfolene and Sulfolane are expected to react with reactive species in vapor phase such as ozone, OH radicals, and UV light. In aqueous conditions, both will also be subject to biotic and abiotic transformation reactions such as ring hydroxylation and hydrolysis of the double bond. This inherent reactivity of Sulfolene is consistent with one of its commercial uses, which is scavenging acids. It applies to both biotic and abiotic chemical reactions and helps explain the strong similarity of physical/chemical and environmental fate and toxicological properties, as described in the following sections.

#### IV. PHYSICOCHEMICAL PROPERTIES

The physical chemical data for Sulfolene provided in Table 2 were primarily obtained from well-established and scientifically accepted reference handbooks such as the Merck Index (O'Neil, 2001) the Industrial Solvents Handbook (Flick, 1985), and Hawley's Condensed Chemical Dictionary (Lewis, 2001), as well as EPIWIN-calculated values

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(USEPA and Syracuse Research Corporation, 2000). These data show that Sulfolene and Sulfolane both are highly water soluble and have similar melting points. The double bond in Sulfolene is expected to impart a slightly higher boiling point and vapor pressure to Sulfolene versus Sulfolane.

**Table 2. Measured (M) and Calculated (C) Physicochemical Properties**

Physical and Chemical Data				
Test	M/C	Sulfolene	M/C	Sulfolane
Melting Point	M <sup>5,7</sup>	63 - 65.5 °C	M <sup>7</sup>	27.4 – 27.8 °C
	M <sup>1</sup>	64.5 °C	M <sup>1</sup>	27.6 °C
	C <sup>2</sup>	17.43 °C	C <sup>2</sup>	16.29 °C
Boiling Point	M <sup>6</sup>	Decomposes	M <sup>7</sup>	285 (bp <sub>760</sub> )
			M <sup>1</sup>	287.3 °C
	C <sup>2</sup>	201.11°C	C <sup>2</sup>	198.49°C
Vapor Pressure			M <sup>5</sup>	14.53 (302 °F); 21.55 (320 °F); 85.23 (392 °F); 115.1 (410 °F); 421.4 (500 °F)
			M <sup>1</sup>	.0062 mmHg (.0083 hPa)
	C <sup>2</sup>	VP: 0.132 mmHg (0.176 hPa)	C <sup>2</sup>	0.004 mmHg (0.0053 hPa)
Kow Partition Coefficient	M <sup>8</sup>	HPLC method < 1.0; Fragment addition Method = -0.8	M <sup>1</sup>	-0.77
	C <sup>3</sup>	-0.45	C <sup>3</sup>	-0.24
Water Solubility	M <sup>5</sup>	5.90 wt% at 25 °C	M <sup>7</sup>	At 30°, miscible with water
	C <sup>4</sup>	2.879 x 10 <sup>5</sup> mg/L	C <sup>4</sup>	1.0 x 10 <sup>6</sup> mg/L

<sup>1</sup>EPIWIN v3.10; measured values from the EPIWIN experimental database.

<sup>2</sup>EPIWIN v3.10; calculated using MPBPWIN v1.40 (determined at 760 millimeter mercury [mmHg]).

<sup>3</sup>EPIWIN v3.10; calculated using KOWWIN v1.66.

<sup>4</sup>EPIWIN v3.10; calculated using WSKOW v1.40.

<sup>5</sup>Flick, 1985.

<sup>6</sup>Lewis, 2001.

<sup>7</sup>O'Neil, 2001.

<sup>8</sup>USEPA, 1991b.

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**Summary:** Adequate data (i.e., Klimisch rating 1 and 2) are available for all endpoints; no additional testing is proposed for the USEPA HPV Challenge Program (see Table 2 and IUCLID documents).

## V. EVALUATION OF ENVIRONMENTAL FATE DATA

Environmental fate data for Sulfolene and Sulfolane were either experimentally measured or estimated using EPIWIN, and are provided in Tables 3, 3a, and 3b. Overall, these substances are expected to be mobile if released to the environment, but will disappear based upon both biotic and abiotic degradation mechanisms and do not pose any bioaccumulation hazard (as described below).

**Table 3. Measured (M) and Calculated (C) Results for Environmental Fate and Pathways**

Environmental Fate and Pathways				
Test	M/C	Sulfolene	M/C	Sulfolane
Photodegradation & Atmospheric Oxidation:			C <sup>4</sup>	Indirect photodegradation – half-life of 9.7 hr
• Ozone Rate Constant	C <sup>1</sup>	20 x 10 <sup>-17</sup> cm <sup>3</sup> /molecule-sec 1.375 Hrs. (at 7x 10 <sup>11</sup> mol/cm <sup>3</sup> )	C <sup>1</sup>	No Data
• Ozone Half Life	C <sup>1</sup>			
• OH Rate Constant	C <sup>1</sup>	65.73 x 10 <sup>-12</sup> cm <sup>3</sup> /molecule-sec 1.953 Hrs	C <sup>1</sup>	13.2 x 10 <sup>-12</sup> cm <sup>3</sup> /molecule-sec 9.666 Hrs
• OH Half Life	C <sup>1</sup>		C <sup>1</sup>	
Stability in Water (Hydrolysis)		No Data	M <sup>4</sup>	Nominal: ca. 1000 mg/L Degradation: no hydrolysis at pH 4, 7, and 9 at 50 ± 1 °C for 5 days
Transport/ Distribution				
Fugacity		See model results below (Table 3a)		See model results below (Table 3b)
Estimated Koc:	C <sup>2</sup>	21.59	C <sup>2</sup>	21.59
Estimated BCF:	C <sup>3</sup>	3.162	C <sup>3</sup>	3.162
Biodegradation	M <sup>5</sup>	2% after 28 days 0% after 28 days	M <sup>4</sup>	10% after 14 days

<sup>1</sup>EPIWIN v3.10; calculated using AOP Program v1.40.

<sup>2</sup>EPIWIN v3.10; calculated using PCKOC Program v1.66.

<sup>3</sup>EPIWIN v3.10; calculated using BCF Program v2.14.

<sup>4</sup>Japan IUCLID, 2003.

<sup>5</sup>USEPA, 1991c.

**Summary:** The weight of evidence in this test plan supports that no further environmental fate testing is necessary to meet HPV SIDS endpoints relating to environmental fate. Adequate data (i.e., Klimsch rating 1 and 2) are available for all endpoints, and no additional testing is proposed for the USEPA HPV Challenge Program (See Table 3 and IUCLID documents).

#### **A. Photodegradation-Atmospheric Oxidation**

Values for Sulfolene photodegradation and atmospheric oxidation were calculated based upon chemical structures using EPIWIN and are shown in Table 3. A calculated half-life for Sulfolene of 1.375 hours and rate constant of  $20 \times 10^{-17}$  cubic centimeter ( $\text{cm}^3$ )/molecule-sec has been estimated for reaction with ozone. EPIWIN was unable to estimate this reaction for Sulfolane due to lack of the carbon/carbon double bond. Also for reaction with hydroxyl radicals, a calculated half-life for Sulfolene of 1.953 hours and a rate constant of  $65 \times 10^{-12}$   $\text{cm}^3$ /molecule-sec has been estimated using EPIWIN, compared to a calculated half-life for Sulfolane of 9.666 hours and a rate constant of  $13.2 \times 10^{-12}$   $\text{cm}^3$ /molecule-sec.

**Summary:** These results show that Sulfolene may be slightly more reactive, but are sufficient for USEPA HPV Challenge Program purposes and no further testing is warranted.

#### **B. Hydrolysis**

Both Sulfolene and Sulfolane are highly water soluble and are stable in solution. EPIWIN was unable to estimate a hydrolysis rate for the functional groups in Sulfolene and Sulfolane. Standard hydrolysis as a function of pH studies of Sulfolane show these materials are stable in water in the pH range of 4-9. pH alone, under the conditions of the standard OECD 111 "Hydrolysis as a function of pH" test, is not sufficient to catalyze hydrolysis of the thiophene ring. Further hydrolytic stability as a function of pH testing will not provide new useful information.

**Summary:** These results show that Sulfolene is not expected to be unstable under the conditions of the standard hydrolysis as a function of pH test. Existing information is sufficient for USEPA HPV Challenge Program purposes and no further hydrolysis testing is warranted.

#### **C. Chemical Transport and Distribution in the Environment (Fugacity Modeling)**

Tables 3a and 3b summarize the Level III Fugacity results for Sulfolene and Sulfolane produced by EPIWIN.

**Table 3a. EPIWIN Level III Fugacity Results for Sulfolene**

Compartment	100% to air	100% to water	100% to soil	Equally to each compartment
Air	69.6%	0.006%	0.03%	0.2%
Water	16.7%	99.8%	21.7%	55.9%
Soil	13.7%	0.001%	78.2%	43.8%
Sediment	0.03%	0.167%	0.04%	0.1%

**Table 3b. EPIWIN Level III Fugacity Results for Sulfolane**

Compartment	100% to air	100% to water	100% to soil	Equally to each compartment
Air	71.1%	0.1%	0.401%	2.93%
Water	16.4%	99.7%	21.7%	54.5%
Soil	12.5%	0.018%	77.8%	42.5%
Sediment	0.03%	0.166%	0.04%	0.1%

**Summary:** Results from the Level III fugacity modeling indicate that releases to water would remain in water while releases to air and soil would partition to water and soil. These results also show that both compounds behave similarly in the environment and further fugacity modeling is not warranted.

#### **D. Biodegradation and Bioaccumulation**

Sulfolene has been tested in two Commission of the European Communities (EC)/OECD Ready Biodegradation tests, the Closed Bottle Test, and the Modified Sturm Test. The results are reliable without restrictions and fulfill the HPV SIDS endpoint for Sulfolene. The results are also in agreement with EPIWIN calculated results. Sulfolene should be inherently biodegradable under real world aerobic and anaerobic conditions. However, under the conservative conditions of the standard OECD ready tests, Sulfolene was shown not to be readily biodegradable.

For additional perspective, the EPIWIN predicted bioconcentration factor (BCF) and organic carbon partition coefficients (K<sub>oc</sub>) are identical and very low for both Sulfolene and Sulfolane, suggesting similar fate profiles in the environment and no bioaccumulation hazard.

**Summary:** Adequate data (i.e., Klimsch rating 1 and 2) are available for all endpoints, and no additional environmental fate testing is proposed for the USEPA HPV Challenge Program (See Table 3 and IUCLID documents).

## **VI. ECOTOXICITY DATA**

Acute fish, daphnid, and algal endpoints for Sulfolene are fulfilled with valid study data. The studies were conducted consistent with relevant OECD and USEPA guidelines. As shown in Table 4, both Sulfolene and its structural surrogate Sulfolane are relatively

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nontoxic to aquatic organisms, and it would have been appropriate to use one structure as a read-across for the other had quality experimental data not been available for Sulfolene.

Aquatic studies have been performed on fish, aquatic invertebrates, and algae; fish appear to be the most sensitive species ( $LC_{50}$  = 940 mg/L for Sulfolene and  $LC_{50}$  > 100 mg/L for Sulfolane). There is also a chronic study available on *Daphnia magna* for Sulfolane.

**Table 4. Results for Ecotoxicity Endpoints**

Ecotoxicity		
Test	Sulfolene	Sulfolane
Acute/Prolonged Toxicity to Fish	96 hr $LC_{50}$ = 940 mg/L <sup>1</sup>	$LC_{50}$ > 100 mg/L <sup>2</sup>
Acute Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	24 hr $EC_{50}$ > 1000 mg/L 48 hr $EC_{50}$ = 800 mg/L <sup>1</sup>	NOEC = 171 mg/L $EC_{50}$ = 852 mg/L <sup>2</sup>
Acute Toxicity to Aquatic Plants (Algae)	$EC_{50}$ (growth rate) > 1000 mg/L <sup>1</sup>	NOEC (biomass) = 171 mg/L; NOEC (growth rate) = 309 mg/L (24-48h); $EC_{50}$ (biomass) = 500 mg/L; $EC_{50}$ (growth rate) > 1000 mg/L <sup>2</sup>
Chronic Toxicity to Aquatic Invertebrates ( <i>Daphnia magna</i> reproduction test)	No Data Available	NOEC = 25.0 mg/L LCEC = 50.0 mg/L $EC_{50}$ = >100 mg/L $LC_{50}$ = >100 mg/L <sup>2</sup>

<sup>1</sup>USEPA, 1991b.

<sup>2</sup>Japan IUCLID, 2003.

**Summary: No additional testing is proposed for ecotoxicity for the USEPA HPV Challenge Program (see Table 4 and IUCLID document).**

## VII. MAMMALIAN TOXICITY

The considerable existing mammalian toxicity information for Sulfolene and Sulfolane demonstrates that these substances share a similar order of toxicity, regardless of the additional double bond in Sulfolene. Mammalian toxicity data demonstrates a low order of toxicity via oral, dermal, and inhalation routes of exposure. Genotoxicity data exist for both Sulfolene and Sulfolane and indicate that genotoxicity is not expected. Repeated dose toxicity testing on both Sulfolene and Sulfolane showed similar results in both rats and mice, and no further repeated dose toxicity testing is required. Sulfolene has not been tested for reproductive and developmental toxicity, but, due to its close structural similarity to Sulfolane, and their common physical, chemical, and toxicological profiles,

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Sulfolene would be expected to be of a similar order of reproductive and developmental toxicity as Sulfolane. Given that Sulfolane is characterized for this endpoint and Sulfolene is expected to produce results of the same order of magnitude, Sulfolane reproductive and developmental toxicity data can be used for read across purposes for Sulfolene, and no further Sulfolene mammalian toxicity testing is warranted to meet OECD SIDS endpoints.

**Table 5. Results for Mammalian Toxicity Endpoints**

<b>Mammalian Toxicity</b>		
<b>Test</b>	<b>Sulfolene</b>	<b>Sulfolane</b>
Acute Oral	3006.5 mg/kg (m) <sup>1</sup> ; 2547.3 mg/kg (f) <sup>1</sup> 2876.1 mg/kg (combined) <sup>1</sup>	2006 mg/kg bw (m) <sup>2</sup> 2130 mg/kg bw (f) <sup>2</sup>
Acute Inhalation	LC <sub>50</sub> : greater than the saturated concentration in air at 25°C. No deaths reported in dose group. <sup>3</sup>	No Data Available
Repeated Dose	<p>Lowest observed adverse effect levels (LOAELs) for weight decrease:</p> <ul style="list-style-type: none"> <li>• Rat: 562 mg/kg/day (m); 178 mg/kg/day (f)<sup>4</sup></li> <li>• Mouse: &gt;3160 mg/kg/day (m); 316 mg/kg/day (f)<sup>4</sup></li> </ul> <p>LOAELs for mortality:</p> <ul style="list-style-type: none"> <li>• Rat: &gt;562 mg/kg/day (m); 316 mg/kg/day (f)<sup>4</sup></li> <li>• Mouse: 1000 mg/kg/day (m); 1000 mg/kg/day (f)<sup>4</sup></li> </ul> <p>No observed adverse effect levels (NOAELs) for weight decrease:</p> <ul style="list-style-type: none"> <li>• Rat: 316 mg/kg/day (m); 100 mg/kg/day (f)<sup>4</sup></li> <li>• Mouse: &gt;3160 mg/kg/day (m); 178 mg/kg/day (f)<sup>4</sup></li> </ul> <p>NOAELs for mortality:</p> <ul style="list-style-type: none"> <li>• Rat: &gt;562 mg/kg/day (m); 178 mg/kg/day (f)<sup>4</sup></li> <li>• Mouse: 562 mg/kg/day (m); 562 mg/kg/day (f)<sup>4</sup></li> </ul>	<p><b>A</b> - NOAEL –</p> <ul style="list-style-type: none"> <li>• 60 mg/kg/day (m); 200 mg/kg/day (f)<sup>2</sup></li> </ul> <p>LOAEL –</p> <ul style="list-style-type: none"> <li>• 200 mg/kg/day (m) - histopathological changes in the kidney); 700 mg/kg/day (f) - suppression of body weight gain and food consumption, and slight increase of GPT value in blood chem.)<sup>2</sup></li> </ul> <p><b>B</b> - NOAEL –</p> <ul style="list-style-type: none"> <li>• 200 mg/kg/day (both)<sup>2</sup></li> </ul> <p>LOAEL –</p> <ul style="list-style-type: none"> <li>• 700 mg/kg/day (both) - death, clinical toxic signs, suppression of body weight gain<sup>2</sup></li> </ul>
Genetic – Gene Mutation	<p><b>A</b> – negative both with and without metabolic activation<sup>5</sup>;</p> <p><b>B</b> – exp. to five graded doses with and without metabolic activation did not increase the reversion to histidine protrophy of five strains of <i>Salmonella typhimurium</i><sup>6</sup></p>	Cytotox - No toxicity up to 5,000 µg/plate in five strains; Genotoxic effects negative both with and without metabolic activation <sup>2</sup>

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Mammalian Toxicity		
Test	Sulfolene	Sulfolane
Genetic – Chromosomal Aberration	Negative with and without metabolic activity <sup>7</sup>	Cytotoxic concentration – 50% growth inhibition not observed at any concentration; Genotoxic effects negative for clastogenicity and polyploidy both with and without metabolic activation <sup>2</sup>
Reproduction/ Developmental Screen	No Data Available	NOAEL (reproductive performance) 700 mg/kg/day (m); 200 mg/kg/day (f) NOAEL (pups toxicity) 60 mg/kg/day <sup>2</sup>  LOAEL – No Data Available <sup>2</sup>

<sup>1</sup> Hazleton, 1982a.

<sup>2</sup> Japan IUCLID, 2003.

<sup>3</sup> USEPA, 1991a.

<sup>4</sup> US Department of Health, Education, and Welfare [HEW], 1978.

<sup>5</sup> Hazleton, 1982c.

<sup>6</sup> Hazleton, 1982d.

<sup>7</sup> Loveday et al., 1990.

**Summary: Data are available for all Mammalian Toxicity endpoints, as provided in Table 5 and described below. No additional testing is proposed for the USEPA HPV Challenge Program.**

#### A. Acute Toxicity

Acute toxicity studies show that Sulfolene is of low acute toxicity by both the oral and inhalation routes (oral LD<sub>50</sub> = 2,876.1 mg/kg [combined male and female]; LC<sub>50</sub> greater than the saturated concentration in air at 25°C) (see Table 5 and IUCLID document). In addition, internal CPChem study summaries for which a full study report could not be located (and therefore were “not assignable” from a data quality perspective) provided the following supporting data for Sulfolene (see Table 5a):

- acute dermal LD<sub>50</sub> of 1,930.4 mg/kg in male rabbits and 1,891.8 mg/kg in female rabbits; and
- acute inhalation LC<sub>50</sub> of 458 ppm in male rats and 418 ppm in female rats.

Importantly, the close structural analogue Sulfolane was also tested and, in general, shows similar if not higher acute toxicity than Sulfolene.

**Table 5a. Supportive Data for Mammalian Toxicity**

<b>Supportive Data for Mammalian Toxicity</b>		
<b>Test</b>	<b>Sulfolene</b>	<b>Sulfolane</b>
Acute Dermal	1930.4 mg/kg (m); 1891.8 mg/kg (f) (Internal CPChem summary only)	1900-3500 mg/kg (male rabbit, subcutaneous) (Andersen et al., 1976)
Acute Inhalation	458 ppm (m); 418 ppm (f) (Internal CPChem summary only)	>12000 mg/m <sup>3</sup> (4 hr) (rat) (Andersen et al., 1977)

**Summary:** These studies fulfill the HPV requirements for the acute toxicity endpoint; no additional testing is proposed for the USEPA HPV Challenge Program.

#### **B. Repeated Dose Toxicity**

Sulfolene has also been tested by the NCI Carcinogenesis Testing Program in a chronic bioassay for possible carcinogenicity (HEW, 1978). As part of that program, a subchronic repeated dose study was performed on both rats and mice to determine dosing ranges for the chronic bioassay. While this study design does not meet OECD and USEPA guidelines, it was conducted under an adequately described protocol, and the study is available for review. The NCI study reported an NOAEL for mortality of 562 mg/kg/day for male rats and 178 mg/kg/day for female rats. In addition, NOAELS for a mortality of 562 mg/kg/day in both male and female mice were reported. These results are similar to the repeated dose toxicity observed with the close structural surrogate Sulfolane, which was tested in accordance with both the Japan Technical Guidance for 28-day repeated dose toxicity testing and OECD Technical Guideline 421.

It should be noted that the Sulfolene Bioassay will also be used as surrogate data for the Sulfolane ICCA HPV program to further support that long-term carcinogenicity effects are unlikely for Sulfolane.

**Summary:** The weight of evidence in this test plan, including the experimentally measured repeated dose toxicity results in rats and mice that agree closely with the repeated dose toxicity results from the structural surrogate Sulfolane, is sufficient to meet this HPV endpoint. No further repeated dose toxicity testing is required (see Table 5 and IUCLID Document).

## C. Genetic Toxicity/Mutagenicity

### 1. Gene Mutation

Gene mutation tests conducted on Sulfolene have consistently resulted in negative results using the Ames Test. Equivalent results were also obtained for Sulfolane.

### 2. Chromosomal Aberrations

*In vitro* chromosomal aberration test results were identified for Sulfolene (Loveday et al, 1990) which showed Sulfolene to be negative for the following categories of chromosomal aberrations:

- “simple,” defined as a chromatid gap, break, fragment, and deletion or chromosome gap, break, or double minuet;
- “complex,” defined as interstitial deletions, triradials, quadriradials, rings, and dicentric chromosomes; and
- “other,” defined as pulverized chromosomes or cells with greater than 10 aberrations.

**Summary:** Several valid *in vitro* genetic toxicity/mutagenicity studies have been performed for Sulfolene, all of which show no mutagenic activity for Sulfolene. Similar data for Sulfolane likewise show a lack of mutagenic activity for these materials. Adequate data are available for this endpoint, and no additional testing is proposed for the USEPA HPV Challenge Program (see Table 5 and IUCLID document).

## D. Reproductive/Developmental Toxicity

Sulfolane was also tested in rats using the reproduction/development screening test pursuant to OECD Technical Guideline 421, with a data quality assessment of Klimisch 1, valid without restriction. The NOAEL for Sulfolane in this study is of the same order of magnitude as the repeated dose study, with an NOAEL for reproductive performance of 700 mg/kg/day in male rats and 200 mg/kg/day in female rats. Also, Sulfolane had an NOAEL of 60 mg/kg/day for production of pups. This study found that the toxic effects for female parents and pups were effects on reproductive parameters such as decrease of the number of estrus cases and increase of dams losing all of their pups. With regard to the pups, toxicity presented as effects on developmental parameters, including the number of pups, viability index, stillbirth, and body weight. No significant effect was observed showing grossly visible abnormalities in the pups.

Sulfolene has not been tested for reproductive and developmental toxicity, but, due to its close structural similarity to Sulfolane, it would be expected to be of a similar order of magnitude as reproductive and developmental toxicity of Sulfolane.

**Summary:** Given that Sulfolane is characterized for this endpoint and is expected to produce results of the same order of magnitude, Sulfolene

**reproductive and developmental toxicity data can be used for read across purposes for Sulfolene. No further Sulfolene testing is warranted to meet OECD SIDS endpoints.**

## **VIII. “BEYOND SIDS” ENDPOINTS**

Studies have been performed on Sulfolene to investigate skin and eye irritation, and skin sensitization potential. A carcinogenicity study was also performed that demonstrated no significant increases in tumors in either sex compared to control groups (see IUCLID Document).

## **IX. CONCLUSIONS**

As summarized below, CPChem concludes that there are sufficient, reliable data on Sulfolene and its structural surrogate, Sulfolane, following a thorough review of company proprietary files, peer-reviewed literature, and/or calculated using widely accepted computer modeling programs. No additional testing is recommended for the USEPA HPV Challenge Program.

**Adequate data (i.e., Klimisch rating 1 and 2) are available for all endpoints; no additional testing is proposed for the USEPA HPV Challenge Program (see Table 2 and IUCLID documents).**

- **PHYSICOCHEMICAL DATA.** Physicochemical endpoints for Sulfolene are fulfilled by using existing measured data or data calculated by the EPIWIN computer model. No additional testing is proposed.
- **ENVIRONMENTAL FATE.** Sufficient data are available to characterize environmental fate for Sulfolene. An estimation from a Level III fugacity model predicts that both Sulfolene, as well as its structural surrogate Sulfolane, will likely partition to soil and water. Ready biodegradation testing showed that Sulfolene and Sulfolane are not readily biodegradable and have very low predicted bioconcentration factors. Organic carbon partition coefficients suggest similar fate profiles in the environment and no bioaccumulation hazard for either Sulfolene or Sulfolane. Sufficient data are available to fulfill the environmental fate endpoints for Sulfolene and no additional testing is proposed.
- **ACUTE AQUATIC TOXICITY.** Scientifically reliable acute aquatic toxicity data are available and indicate that Sulfolene is relatively nontoxic to aquatic organisms. Sufficient data are available to fulfill the acute aquatic toxicity endpoint for Sulfolene and no additional testing is proposed.
- **ACUTE MAMMALIAN TOXICITY.** Mammalian toxicity data demonstrates a low order of toxicity via oral, dermal, and inhalation routes of exposure. Sufficient data are available to fulfill the acute toxicity endpoint for Sulfolene and no additional testing is proposed.

- **GENETIC TOXICITY.** Genotoxicity data exist for both Sulfolene and Sulfolane and indicate that genotoxicity is not expected. Sufficient data are available to fulfill the genetic toxicity endpoint for Sulfolene and no additional testing is proposed.
- **REPEATED DOSE TOXICITY.** Repeated dose toxicity testing on both Sulfolene and Sulfolane showed similar results in both rats and mice, and no further repeated dose toxicity testing is required.
- **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY.** Sulfolene has not been tested for reproductive and developmental toxicity, but, due to its close structural similarity to Sulfolane, it would be expected to be of a similar order of magnitude as Sulfolane. Given that Sulfolane is characterized for this endpoint and is expected to produce results of the same order of magnitude, Sulfolane can be used as a structural surrogate for Sulfolene, and no further Sulfolene testing is warranted for this endpoint.

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### **Appendix III**

#### **DATA QUALITY ASSESSMENT**

Available environmental, ecotoxicity, and mammalian toxicity studies were reviewed and assessed for reliability according to standards specified by Klimisch et al., (1997), as recommended by the USEPA (1999a) and the OECD (OECD, 2002). The following reliability classification (Klimisch rating) has been applied to each study assessed:

- *1 = Reliable without Restriction* – Includes studies that comply with USEPA- and/or OECD-accepted testing guidelines and were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented;
- *2 = Reliable with Restriction* – Includes studies that were conducted according to national/international testing guidance and are well documented. May include studies that were conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters that are well documented and scientifically valid but vary slightly from current testing guidance. Also included in this category were physical-chemical property data obtained from reference handbooks, as well as environmental endpoint values obtained from an accepted method of estimation (e.g., USEPA's EPIWIN estimation program);
- *3 = Not Reliable* – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or in which documentation is insufficient; and,
- *4 = Not Assignable* – This designation is used in this dossier for studies that appear scientifically valid but for which insufficient information is available to adequately judge robustness.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this dossier. Those key studies selected for inclusion are considered typical of the endpoint responses observed in other studies of a similar nature and design that were identified during our search of the literature.